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Relationship between nodule count and lung cancer probability in baseline CT lung cancer screening: The NELSON study

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ABSTRACT

Objectives: To explore the relationship between nodule count and lung cancer probability in baseline low-dose CT lung cancer screening.

Materials and Methods: Included were participants from the NELSON trial with at least one baseline nodule (3392 participants [45% of screen-group], 7258 nodules). We determined nodule count per participant. Malignancy was confirmed by histology. Nodules not diagnosed as screen-detected or interval cancer until the end of the fourth screening round were regarded as benign. We compared lung cancer probability per nodule count category.

Results: 1746 (51.5%) participants had one nodule, 800 (23.6%) had two nodules, 354 (10.4%) had three nodules, 191 (5.6%) had four nodules, and 301 (8.9%) had > 4 nodules. Lung cancer in a baseline nodule was diagnosed in 134 participants (139 cancers; 4.0%). Median nodule count in participants with only benign nodules was 1 (Inter-quartile range [IQR]: 1–2), and 2 (IQR 1–3) in participants with lung cancer (p = NS). At baseline, malignancy was detected mostly in the largest nodule (64/66 cancers). Lung cancer probability was 62/1746 (3.6%) in case a participant had one nodule, 33/800 (4.1%) for two nodules, 17/354 (4.8%) for three nodules, 12/191 (6.3%) for four nodules and 10/301 (3.3%) for > 4 nodules (p = NS).

Conclusion: In baseline lung cancer CT screening, half of participants with lung nodules have more than one nodule. Lung cancer probability does not significantly change with the number of nodules. Baseline nodule count will not help to differentiate between benign and malignant nodules. Each nodule found in lung cancer screening should be assessed separately independent of the presence of other nodules.

1. Introduction

In 2011, the National Lung Screening Trial (NLST) reported a 15–20% reduction in lung cancer mortality among individuals screened by annual low-dose CT, if compared to participants screened by annual chest X-ray [1]. Following the publication of this positive result, adapted guidelines were published, all recommending lung cancer screening in a high-risk population [2–5]. A remaining problem in lung cancer screening, however, is the high rate of false-positive screen results.

In CT lung cancer screening trials, about half of screened participants have pulmonary nodules, the overwhelming majority being benign [1,6,7]. A key issue in lung cancer screening is to differentiate benign and malignant nodules at an early stage. Several radiological

Abbreviations: CT, computed tomography; CI, confidence interval; IQR, inter-quartile range; NELSON, Dutch-Belgian randomized lung cancer screening trial; NLST, National Lung Screening Trial; PanCan, Pan-Canadian Early Detection of Lung Cancer Study

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features, such as size, growth rate, morphology, and location are associated with an increased lung cancer probability and may help radiologists in adequately identifying a high-risk baseline nodule [8,9].

A commonly overlooked aspect is the number of nodules per screenee (nodule count) at the time of nodule detection. Generally, nodule management in lung cancer screening is based on the largest or most suspicious nodule, but often more than one nodule is present. While only limited data concerning the impact of nodule count on lung cancer probability is available, one study indicated a negative linear relationship between nodule count and lung cancer probability and incorporated it in a risk calculator for nodules detected at baseline screening [10].

However, in a preliminary, limited analysis on multinodularity and lung cancer probability for nodules detected in the first and second screening round of the Dutch-Belgian Randomized Lung Cancer Screening Trial (acronym NELSON), the relationship between nodule count and lung cancer probability in participants was found to be ambiguous, with varying lung cancer probabilities as nodule count increased [7]. The purpose of this study was to explore in-depth the relationship between nodule count and lung cancer probability in the baseline round of the NELSON trial.

2. Materials and methods

2.1. NELSON trial and study participants

The NELSON trial was designed to investigate whether low-dose spiral CT screening will decrease 10-year lung cancer mortality by at least 25% in high-risk (ex-) smokers. The Dutch Minister of Health and the ethics board of each participating center approved the NELSON trial. All participants gave written informed consent. The design of the NELSON trial, including participant selection and lung nodule management has been published [11,12]. In brief, 15,792 current and former smokers [13], aged 50–75 years, who smoked $>$ 15 cigarettes daily for over 25 years or $>$ 10 cigarettes daily for over 30 years were included. Participants were randomized 1:1 to usual care without screening or screening. Between April 2004 and December 2006, 7557 participants underwent baseline screening. Baseline screening was performed in year 1, and incident screening rounds took place in year 2 (second round), year 4 (third round), and year 6.5 (fourth round). For this retrospective analysis, we included all participants with non-calcified nodules detected at baseline. We included all nonsolid, part-solid and solid nodules with volume $\geq 15\ mm^3$ and/or sub-solid diameter $\geq$ 4 mm (study detection limits).

2.2. Lung cancer screening CT scan protocol, reading and data set

Participants were invited to one of four screening sites each using a 16-multidetector CT scanner (three Sensation-16 systems, Siemens Medical Solutions, Forchheim, Germany and one Brilliance 16P system, Philips Medical Systems, Cleveland, OH, USA). A non-contrast low-dose CT scan of the entire chest was obtained in a cranio-caudal direction in one breath-hold (about 12 s in spiral mode with 16 × 0.75 mm collimation and pitch 1.3). Typical technical parameters for the low-dose setting depended on body weight ($<$ 50 kg, 50–80 kg and $>$ 80 kg): 80–90 kVp, 120 kVp and 140 kVp respectively [11]. Image data sets with isotropic voxels were available, allowing analyses with software for semi-automated volume measurements (Syngo LungCARE, Siemens Healthcare, Erlangen, Germany). All images were read by two independent radiologists with experience in chest CT reading ranging between 1 and 20 years, and in case of discrepancy a third, expert reader made the final decision [11,14]. Radiologists could overrule a protocol-based screening result (done for 6% of participants at the baseline screening round) and manually adjust the volume measurement in case of inappropriate segmentation [14]. Nodule management was based on size, density and growth rate of the largest nodule. The nodule size criteria were published before [11]. In short, NODCAT 2 comprised solid nodules with volume 15–50 mm^3 and subsolid nodules with diameter 4–8 mm, and led to a negative screen result (invitation for regular next screening round). NODCAT 3 were solid nodules with volume 50–500 mm^3 and subsolid nodules $\geq$ 8 mm. NODCAT 4 nodules were defined as potentially malignant (solid, $>$ 500 mm^3, positive screen result), and required immediate referral to the pulmonologist for work-up. NODCAT 3 nodules were assigned an indeterminate test result, requiring a repeat scan after 3–4 months to assess nodule growth. Growth was defined as change in volume of $>$ 25% and volume doubling-time was calculated as described previously [11,15]. Screenees having a nodule with volume doubling time $<$ 400 days (fast growing, positive screen result) were referred to a pulmonologist for work-up.

2.3. Nodule characteristics

Both readers reported information regarding nodule volume, location, distance to costal pleura and margin. Nodule location was defined as upper lobe (middle, left or right upper lobe) or lower lobe (left or right lower lobe). In case of distance to costal pleura less than one-third of the total distance of hilum-costal pleura, nodules were considered to be peripheral, and with more than one-third of the total distance, nodules were considered to be non-peripheral. Nodule margin was classified as smooth, lobulated, spiculated or irregular [16].

2.4. Nodule count

Nodule count was defined as the number of non-calcified lung nodules present in the baseline screening round. We compared nodule count at baseline for participants with only benign nodules and participants with lung cancer. Five categories based on nodule count were defined: 1 nodule, 2 nodules, 3 nodules, 4 nodules and $>$ 4 nodules. Histology was the reference for diagnosis. In case a nodule was not diagnosed as screen-detected lung cancer or interval cancer until the end of the fourth screening round, the nodule was regarded as benign.

2.5. Statistical analysis

Descriptive statistics were reported as numbers and percentages. We tested data distribution with normality plots. Normally distributed variables were described by mean and 95% confidence interval (95%-CI), while non-normally distributed variables were described by median and inter-quartile range (IQR). We assessed the relationship of participant age and smoked pack-years with nodule count by using Spearman's rank correlation coefficient. We derived lung cancer probability per screenee and per nodule for categories based on number of baseline nodules, by dividing the number of lung cancer cases per category by number of screenees and number of nodules, respectively. We tested the relationship between the presence of lung cancer and the number of baseline nodules by using chi-square. We used SPSS Statistics version 22 (IBM, Armonk, NY) for all analyses, and considered a p-value of $<$ 0.05 as statistically significant.

3. Results

3.1. Characteristics of study population

In this study, we included 3392 participants with 7258 non-calcified baseline nodules (45% of all screen-group participants). Median participant age was 58 years (IQR 55–63 years); 84.4% (2863/3392) were male (Table 1). In total, 1746 participants (51.5%) had one nodule, 800 (23.6%) had two nodules, 354 (10.4%) had three nodules, 191 (5.6%) had four nodules, and 301 (8.9%) had five or more nodules. Fig. 1 shows the distribution of nodule count per participant.

The percentage of screenees with actionable nodules (NODCAT 3 or

Table 1
Characteristics of participants with at least one pulmonary nodule at baseline screening round.

		All participants N = 3,392	1 Nodule N = 1,746	2 Nodules N = 800	3 Nodules N = 354	4 Nodules N = 191	> 4 Nodules N = 301
Age	Median	58	58	59	59	59	59
	IQR	55–63	54–63	55–63	55–63	55–64	55–63
Pack Years	Median	38.0	37.9	38.7	37.9	38.7	37.9
	IQR	29.7–49.5	29.7–49.5	29.7–49.5	29.7–49.5	31.2–53.2	29.7–49.5
Gender	Male N (%)	2,863 (84.4)	1,455 (83.3)	674 (84.3)	298 (84.2)	169 (88.5)	267 (88.7)
NODCAT_max[a]	2, N (%)	1,616 (47.6)	1,109 (63.5)	333 (41.6)	106 (29.9)	38 (19.9)	30 (10)
	3, N (%)	1,588 (46.8)	570 (32.6)	416 (52.0)	219 (61.9)	134 (70.2)	249 (82.7)
	4, N (%)	188 (5.5)	67 (3.8)	51 (6.4)	29 (8.2)	19 (9.9)	22 (7.3)

[a] Largest nodule at baseline screening. A NODCAT 2 nodule is solid nodules with volume 15–50 mm^3 or sub-solid with diameter 4–8 mm, a NODCAT 3 nodule is solid with volume 50–500 mm^3, or sub-solid ≥8 mm, and a NODCAT 4 nodule is solid > 500 mm^3.

4; short-term follow-up or referral) increased linearly with the number of baseline nodules, from 36.4% to 90.0% (Table 1). Spearman's correlation coefficient showed slightly more nodules by increasing age (correlation coefficient 0.044; p = 0.01). No difference was found in number of nodules by smoked pack-years (correlation coefficient 0.026; p = 0.13).

3.2. Description of cancers in study population

During four screening rounds, 139 baseline nodules in 134 participants were proven to be lung cancer. Simultaneous double tumours were found in five participants. Of the 139 cancers, 70 were diagnosed to be malignant immediately after the baseline round (66 screenees). At baseline, lung cancer was histologically confirmed in the largest nodule in 64/66 (97.0%) screenees (double tumours counted once), and in the second largest detected nodule in 2/66 (3.0%) cases. In later rounds, 49/56 (87.5%) screen-detected lung cancers and 10/12 (83.3%) interval cancers were found in baseline nodules that were the largest at the baseline CT. On population basis, median nodule count was 1 (IQR 1–2) in participants with only benign nodules, and 2 (IQR 1–3) in participants with lung cancer. Range of nodule count was equal for participants with only benign nodules and participants with lung cancer (1–18 nodules).

3.3. Nodule characteristics

Baseline nodules most often were located in the lower lobes, in the periphery of the lung, and had a smooth shape. Compared to benign baseline nodules, malignant nodules were larger and more often sub-solid, had more often a non-smooth margin, and were more often located in the upper lobes of the lung. Nodule characteristics per nodule count are shown in Table 2.

3.4. Lung cancer probability: participant-based analysis

In 62 of 1746 participants with one baseline nodule (3.6%; 95% CI, 2.8-4.6%), the solitary nodule was lung cancer. Of 800 participants with two lung nodules, 33 (4.1%; 95% CI, 2.9-5.8%) were diagnosed with lung cancer in one of these nodules. In 17 of 354 participants with three nodules (4.8%; 95% CI, 2.9-7.7%), 12 of 191 participants with four nodules (6.3%; 95% CI, 3.4-11.0%), and ten of 301 participants with at least five nodules (3.3%; 95% CI, 1.7-6.2%), lung cancer was diagnosed (Table 3). Lung cancer probability did not differ significantly for the different nodule count categories (p = 0.34).

Of the 12 participants with a baseline nodule diagnosed as interval cancer, three participants had a single baseline nodule, five had two nodules at baseline, two had three baseline nodules, one had four and one had > 4 nodules at baseline.

3.5. Lung cancer probability: nodule-based analysis

Lung cancer probability per nodule was 3.6% in case of one nodule, 2.1% in case of two nodules, 1.8% in case of three nodules, 1.7% in case of four nodules and 0.7% in case of screenees with more than four nodules.

Table 4 shows an increasing lung cancer risk in increasing nodule categories (overall; NODCAT 2 0.3%, NODCAT 3 2.5% and NODCAT 4 30.1%). There was no difference in lung cancer probability for a NODCAT 2 nodule found in screenees with only one nodule or screenees with a higher nodule count. For actionable nodules

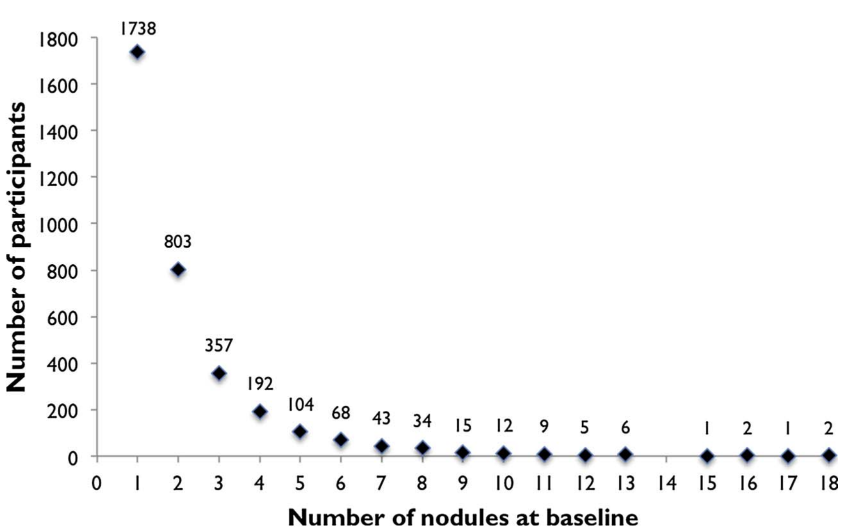

Fig. 1. Distribution of nodule count in 3389 participants at baseline lung cancer screening.

Table 2
Nodule characteristics detected at baseline screening round.

Number of Nodules		1 Nodule	2 Nodules	3 Nodules	4 Nodules	> 4 Nodules	*Benign*	*Malignant*	*P-value*
Volume (mm^3)[a]	Median	36.9	38.3	38.3	38.6	38.9	*37.7*	*328.6*	*< 0.001*
	IQR	23.8–69.0	24.1–70.3	25.1–70.1	24.9–71.6	24.6–67.5	*24.2–67.3*	*112.7–1130.5*	
NodCat	2	959 (64.0)	972 (62.0)	707 (63.5)	476 (62.3)	1444 (62.4)	*4545 (63.8)*	*13 (9.4)*	*< 0.001*
	3	484 (32.3)	537 (34.2)	374 (33.6)	263 (34.4)	834 (36.0)	*2430 (34.1)*	*64 (46.0)*	
	4	55 (3.7)	60 (3.8)	32 (2.9)	25 (3.3)	36 (1.6)	*144 (2.0)*	*62 (44.6)*	
Nodule Type[b]	Solid	1439 (96.8)	1504 (96.5)	1074 (96.7)	744 (97.4)	2277 (98.6)	*6915 (97.5)*	*123 (88.5)*	*< 0.001*
	Part-solid	15 (1.0)	27 (1.7)	18 (1.6)	8 (1.0)	11 (0.5)	*72 (1.0)*	*7 (5.0)*	
	Nonsolid	33 (2.2)	28 (1.8)	19 (1.7)	11 (1.4)	21 (0.9)	*103 (1.5)*	*9 (6.5)*	
Location[c,d]	Upper Lobe	569 (38.6)	620 (40.0)	381 (34.9)	276 (34.9)	760 (34.2)	*2517 (36.2)*	*89 (64.0)*	*< 0.001*
	Lower lobe	906 (61.4)	929 (60.0)	712 (65.1)	472 (63.1)	1465 (65.8)	*4434 (63.8)*	*50 (36.0)*	
	Peripheral	1204 (81.6)	1252 (80.7)	923 (83.2)	623 (81.9)	1983 (86.1)	*5872 (83.1)*	*113 (81.9)*	*0.73*
	Non-peripheral	271 (18.4)	300 (19.3)	186 (16.8)	138 (18.1)	321 (13.9)	*1191 (16.9)*	*25 (18.1)*	
Shape[e]	Non-smooth	89 (6.9)	108 (7.8)	67 (6.9)	30 (4.8)	65 (3.1)	*299 (4.9)*	*60 (45.5)*	*< 0.001*
	Smooth	1206 (93.1)	1276 (92.2)	903 (93.1)	594 (95.2)	1920 (96.7)	*5827 (95.1)*	*72 (54.5)*	

Unless otherwise indicated, data are numbers of nodules, with percentages in parenthesis. Abbrevations: IQR– Interquartile range.
[a] In 193/7258 (2.7%) no volume measurement was possible, for instance in sub-solid nodules.
[b] In 29/7258 (0.4%) nodule type was not specified, mostly due to very small nodule size ($< 50\,mm^3$).
[c,d] In 225/7258 (3.1%) location was not specified (168/7258 (2.3%) peripheral versus non peripheral and 57/7258 (0.8%) upper versus lower lobe).
[e] In 1000/7258 (13.8%) nodule shape was not specified, mostly due to very small nodule size ($< 50\,mm^3$).

($> 50\,mm^3$; NODCAT 3 or 4), the risk of malignancy in a particular nodule decreased in case a nodule was found in screenees with four or more nodules per screenee, compared to actionable nodules found in screenees with only one nodule ($p < 0.001$ for NODCAT 3 and $p < 0.05$ for NODCAT 4 nodules).

4. Discussion

With the use of multi-detector low dose CT scanners (very) small lung nodules can be detected, the minority being malignant. Whether the number of lung nodules (nodule count) plays a role in the determination of lung cancer probability still remains largely unknown. This study shows that at baseline CT lung cancer screening, nearly half of screening participants with lung nodules have more than one lung nodule (1746/3392 [51.5%]), representing about one-fourth of all screenees. We found no statistically significant relationship between nodule count and lung cancer probability in participants with baseline nodules. We observed a non-significant trend whereby lung cancer probability increased as a function of nodule count, with a peak in lung cancer probability in subjects with four baseline nodules (6.3%). However, this non-significant increasing trend did not continue. The implications of these findings partly differ from previous observations by McWilliams et al., where nodule count was incorporated in a model for the prediction of malignancy in pulmonary nodules [10]. In their risk calculator, they found a linear reduction of a baseline nodule's lung cancer probability with an increased number of pulmonary nodules per screenee.

Table 4
Lung cancer probability by nodule count for NODCAT* 2–4 nodules.

Baseline NODCAT	NODCAT 2 Nodules		NODCAT 3 Nodules		NODCAT 4 Nodules	
Cancer	Yes	No	Yes	No	Yes	No
Overall cancer	*13 (0.3)*	*4545 (99.7)*	*64 (2.6)*	*2431 (97.4)*	*62 (30.1)*	*144 (69.9)*
Nodule count 1	6 (0.5)	1102 (99.5)	29 (5,1)	543 (94.9)	27 (40.9)	39 (59.1)
Nodule count 2	4 (0.4)	988 (99.6)	16 (2.9)	536 (97.1)	15 (26.8)	41 (73.2)
Nodule count 3	3 (0.4)	682 (99.6)	9 (2.6)	334 (97.4)	7 (20.6)	27 (79.4)
Nodule count 4	0 (0)	471 (100)	7 (2.6)	265 (97.4)	6 (28.6)	15 (71.4)
Nodule count > 4	0 (0)	1302 (100)	3 (0.4)	753 (99.6)	7 (24.1)	22 (75.9)

Note − Data are numbers of nodules, with percentages in parenthesis.

In our subgroup of the NELSON study containing all participants with non-calcified baseline nodules, we found lung cancer in a baseline nodule in 134/3392 (4.0%) participants, up to six years after baseline (information regarding new nodules was published elsewhere [17]). In the PanCan study, the overall rate of malignancy was 5.5%. In comparison to the findings of McWilliams et al. [10], we found a much lower mean nodule count per screened participant. The subjects with benign nodules in the PanCan study had a mean of 6.2 nodules, compared to 2.1 nodules (median 1 nodule) in our study. In the PanCan

Table 3
Lung cancer probability with 95% confidence intervals on participant basis: cancer detection at baseline versus at later screening rounds.

Nodule Count	Participants	Total Cancer	Lung cancer probability	95% CI	Baseline Cancer	Lung cancer probability Baseline	95% CI Baseline	Cancer in later round*	Lung cancer probability Incidence round	95% CI Incidence round
1 Nodule	1746	62	3.6%	2.8–4.6%	30	1.7%	1.2–2.5%	32	1.8%	1.3–2.6%
2 Nodules	800	33	4.1%	2.9–5.8%	17	2.1%	1.3–3.5%	16	2.0%	1.2–3.3%
3 Nodules	354	17	4.8%	2.9–7.7%	6	1.7%	0.7–3.8%	11	3.1%	1.6–5.7%
4 Nodules	191	12	6.3%	3.4–11.0%	7	4.2%	2.0–8.4%	5	2.6%	1.0–6.3%
> 4 Nodules	301	10	3.3%	1.7–6.2%	6	2.0%	0.8–4.5%	4	1.3%	0.4–3.6%
Total	*3392*	*134*	*4.1%*	*3.4–4.8%*	*66*	*2.0%*	*1.5–2.5%*	*68*	*2.0%*	*1.6–2.6%*

Note − Data are numbers of participants, with percentages in parenthesis.
Abbreviations: 95% CI − 95% confidence interval.
* lung cancer diagnosed in a nodule already present at baseline.

study, subjects with lung cancer had a mean of 4.8 nodules, in contrast to our findings of 2.3 nodules on average (median 2 nodules). Differences may be explained by differences in inclusion criteria for screenees. The NELSON study recruited participants aged 50–75 years without a history of lung cancer, who smoked > 15 pack-years. The PanCan study used a different approach for recruiting participants, namely via a risk-prediction model [18]. Participants with an estimated risk of developing lung cancer in the next 3 years of ≥ 2% were included. Geographical differences in pulmonary nodule nature (i.e. prevalence of fungus infestations [19]) may have influenced the number of nodules in these studies on two different continents as well.

In 64/66 (97.0%) of participants with lung cancer detected at baseline, malignancy was detected in the nodule with the largest volume. This contrasts with the results by McWilliams et al. [10], who showed that in one-fifth of the participants, the largest nodule was not the one that turned out to be malignant at baseline or follow-up. This discrepancy might be explained by the use of semi-automated, volumetric measurement in our study, while manual, two-dimensional diameter measurements were performed in the PanCan study. Previously, it has been shown that nodule measurements are more accurate with volumetric techniques compared to diameter techniques [20–22]. Possibly, diameter measurements cannot identify the largest nodule as good as volumetry.

The American College of Radiology's Lung Imaging Reporting and Data System (Lung-RADS) proposed to classify screening CTs by the nodule with highest malignant risk (usually the largest nodule) [23]. Our results confirm this policy. Each nodule found in lung cancer screening subjects should be assessed separately whereby the largest nodule has the highest probability to be malignant.

While reporting and measuring all lung nodules might be time consuming, it is important to lung cancer screening for two reasons. First, new nodules are regularly found after baseline screening and were shown to carry a higher lung cancer probability than do baseline nodules even at smaller size [24]. To ensure the appropriate detection of new nodules, previously present nodules need to be well documented. Secondly, after initial detection a nodule's risk-stratification relies on growth assessment which is based on the size difference between two scans and therefore the previous measurements [7,25].

We found that the more nodules per screenee, the greater the likelihood that the largest nodule was classified as indeterminate (NODCAT 3, see Table 1). Indeterminate pulmonary nodules led to an extra follow-up CT examination after 3 months. Therefore, the more nodules per screenee, the more follow-up scans were made to assess growth.

Higher age and number of smoked pack-years are associated with an increased risk of developing lung cancer [10]. In our analysis, higher age at baseline was correlated with a slightly increased risk of having more pulmonary nodules. In contrast, no relationship was found between nodule count at baseline and number of smoked pack-years.

We included all non-calcified nodules, and did not differentiate between solid, part- solid and pure nonsolid nodules. More detailed research on the influence of multiple nodules from different subtypes (solid, sub-solid) on lung cancer probability is recommended. Furthermore, external validation of the nodule count and lung cancer probability in high-risk screening participants needs to be performed to confirm our findings.

4.1. Conclusion

At baseline CT lung cancer screening, nearly half of screened participants with lung nodules have more than one lung nodule, representing a quarter of all screenees. Lung cancer probability did not significantly change with number of nodules, therefore baseline nodule count proved to be not useful for prediction of malignancy. Each nodule found in lung cancer screening subjects should be assessed separately independent of the presence of other nodules.

Summary conflicts of interest statements

MAH, JEW, RBP, GHdB, UY-K, HJMG, CMvdA, KN, PMAvO, MO, RV have nothing to disclose. HJdK reported: 'Health Technology Assessment for CT Lung Cancer Screening in Canada'. Cancer Care Ontario, dr. Paszat. Grant. HJdK took part in a 1-day advisory meeting on biomarkers organized by M.D. Anderson/Health Sciences during the 16th World Conference on Lung Cancer. HJdK received a grant from the University of Zurich to assess the cost-effectiveness of computed tomographic lung cancer screening in Switzerland.

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